

Serial No.: 09/405,046  
Filed: 27 September 1999

18. An MRI agent according to claim 12, 13, or 14 wherein said peptide inhibits a protease.
19. An MRI agent according to claim 18 wherein said protease is selected from the group consisting of caspase, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase.

### REMARKS

Claims 1-19 are pending. An appendix of pending claims is attached for the Examiner's convenience.

Support for new claims 12, 13, 14 and 17 is found at least on page 15, beginning at line 8, through page 16, ending line 15; page 20, lines 8-26; pages 28-29; and, page 32, lines 1-13. Support for new claims 15 and 16 is found on at least on page 29, lines 4-18. Support for new claim 18 is found at least on page 22, lines 25-27 and on page 23, lines 1-5. Support for new claim 19 is found at least on page 22, lines 10-23.

The Commissioner is authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-1300 (our Order No. A-58634-6/RFT/RMS/RMK).

Dated: June 21, 2000

Respectfully submitted,

FLEHR HOHBACH TEST  
ALBRITTON & HERBERT LLP

By: [Signature]

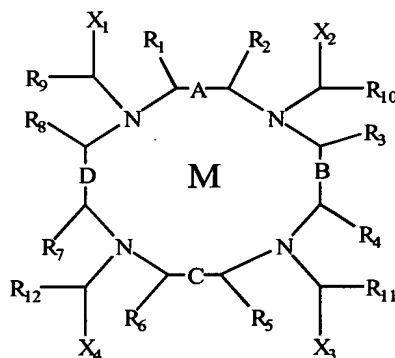
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Serial No.: 09/405,046  
Filed: 27 September 1999

### Appendix of Pending Claims

1. An MRI agent comprising:
  - a) a Gd(III) ion bound to a chelator such that said Gd(III) ion has coordination atoms in at least 5 coordination sites of said Gd(III) ion;
  - b) a blocking moiety covalently attached to said chelator which hinders the rapid exchange of water in the remaining coordination sites;wherein said blocking moiety is capable of interacting with a target substance such that the exchange of water in the remaining coordination sites is increased.
2. An MRI agent having the formula:



wherein

M is a paramagnetic metal ion selected from the group consisting of Gd(III), Fe(III), Mn(II), Yt(III), Cr(III) and Dy(III);

A, B, C and D are either single bonds or double bonds;

X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are -OH, -COO-, -CH<sub>2</sub>OH -CH<sub>2</sub>COO-, or a blocking moiety;

R<sub>1</sub> - R<sub>12</sub> are hydrogen, alkyl, aryl, phosphorus moiety, or a blocking moiety;

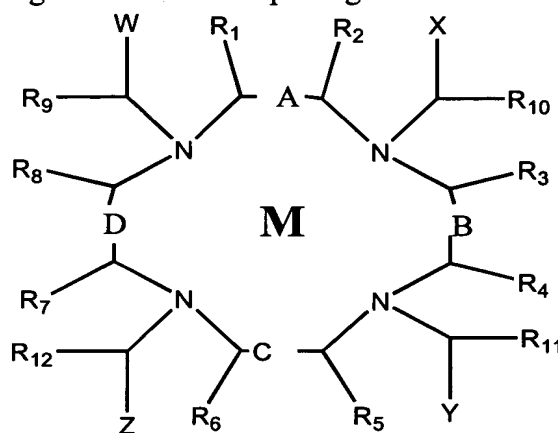
wherein at least one of X<sub>1</sub>-X<sub>4</sub> and R<sub>1</sub> - R<sub>12</sub> is a blocking moiety.

**Serial No.:** 09/405,046  
**Filed:** 27 September 1999

3. An MRI agent comprising:
  - a) at least a first paramagnetic metal ion bound to a first complex, said first complex comprising:
    - i) a first chelator; and
    - ii) a blocking moiety covalently attached to said first chelator which binds in at least a first coordination site of said first metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site of said first metal ion is increased; and
  - b) at least a second paramagnetic metal ion bound to a second complex, said second complex comprising:
    - i) a second chelator; and
    - ii) a blocking moiety covalently attached to said second chelator which binds in at least a first coordination site of said second metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site of said second metal ion is increased.
4. An MRI agent comprising at least a first MRI duplex moiety comprising:
  - a) a first chelator comprising a first paramagnetic metal ion;
  - b) a second chelator comprising a second paramagnetic metal ion;
  - c) a blocking moiety covalently attached to at least one of said first or said second chelators, said blocking moiety providing at least a first coordination atom of each of said first and said second metal ions and which is capable of interacting with a target substance such that the exchange of water in at least a first coordination site in at least one of said metal ions is increased.
5. A composition comprising a polymer comprising at least one covalently linked MRI contrast agent comprising a paramagnetic metal ion bound to a complex, said complex comprising:
  - a) a chelator; and
  - b) a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased.
6. A MRI agent comprising a paramagnetic metal ion bound to a complex, said complex comprising:
  - a) a chelator; and
  - b) a blocking moiety covalently attached to said chelator which binds in at least a first coordination site of said metal ion and which is capable of interacting with a target substance such that the exchange of water in at least said first coordination site is increased.

Serial No.: 09/405,046  
Filed: 27 September 1999

7. A MRI agent comprising  
a) a paramagnetic metal ion capable of binding  $n$  coordination atoms, wherein said metal ion is bound to a chelator such that said metal ion has coordination atoms at  $(n-1)$  or  $(n-2)$  coordination sites of said metal ion; and  
b) a blocking moiety covalently attached to said chelator that hinders the rapid exchange of water in the remaining coordination site or sites,  
wherein said blocking moiety is capable of interacting with a target substance, such that the exchange of water at the remaining coordination site or sites is increased.
8. A MRI agent having the formula comprising:



wherein

M is a paramagnetic metal ion selected from the group consisting of Gd(III), Fe(III), Mn(II), Yt(III), Cr(III) and Dy(III);

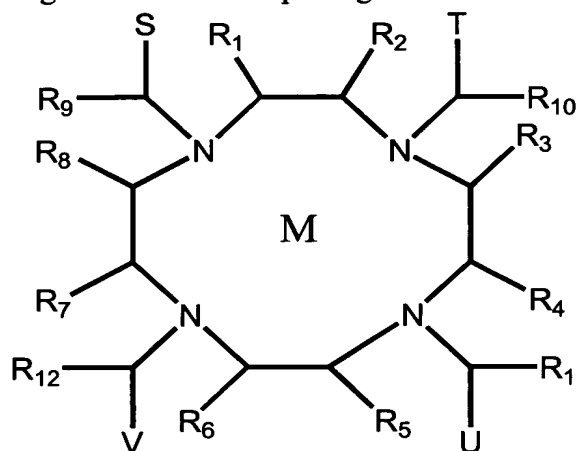
A, B, C and D are either single bonds or double bonds;

W, X, Y and Z are -OH, -COO-, -CH<sub>2</sub>OH or -CH<sub>2</sub>COO-;

R<sub>1</sub> - R<sub>12</sub> are hydrogen, alkyl, substituted alkyl, phosphorus moiety, or a blocking moiety;  
wherein at least one of R<sub>1</sub> - R<sub>12</sub> is a blocking moiety.

Serial No.: 09/405,046  
 Filed: 27 September 1999

9. A MRI agent having the formula comprising:



wherein

M is a paramagnetic metal ion selected from the group consisting of Gd(III), Fe(III), Mn(II), Yt(III), Cr(III) and Dy(III);

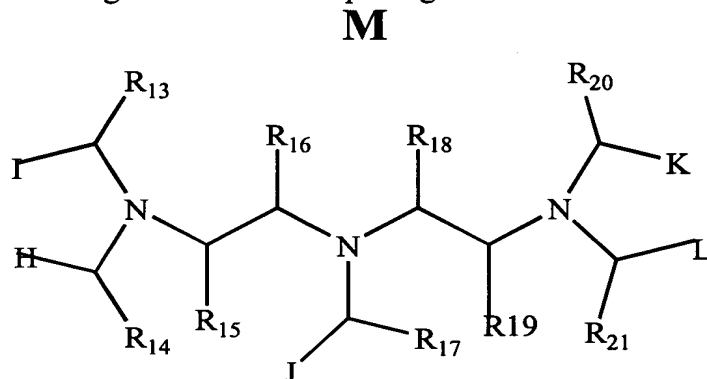
A, B, C, and D are either single or double bonds;

S, T, U and V are -OH, -COO-, -CH<sub>2</sub>OH, -CH<sub>2</sub>COO-, or a blocking moiety;

R<sub>1</sub> - R<sub>12</sub> are hydrogen, alkyl, substituted alkyl, or phosphorus moiety;

wherein at least one of S, T, U or V is a blocking moiety.

10. A MRI agent having the formula comprising:



wherein

M is a paramagnetic metal ion selected from the group consisting of Gd(III), Fe(III), Mn(II), Yt(III), Cr(III) or Dy(III);

H, I, J, K and L are -OH, -COO-, -CH<sub>2</sub>OH, -CH<sub>2</sub>COO-, or a blocking moiety;

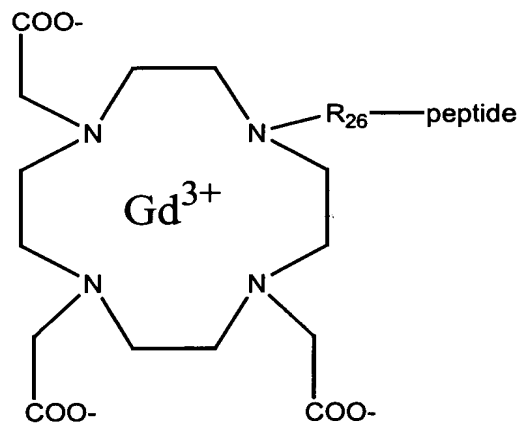
R<sub>13</sub> - R<sub>21</sub> are hydrogen, alkyl, substituted alkyl, phosphorus moiety or a blocking moiety;

wherein at least one of R<sub>13</sub> - R<sub>21</sub>, H, I, J, K or L is a blocking moiety.

11. A method of magnetic resonance imaging of a cell, tissue or patient comprising administering an MRI agent according to claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 to a cell, tissue or patient and rendering a magnetic resonance image of said cell, tissue or patient.

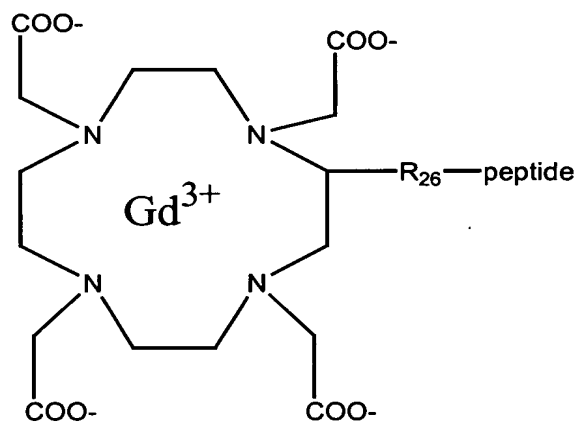
Serial No.: 09/405,046  
Filed: 27 September 1999

12. An MRI agent according to claim 1 having the formula:



wherein  $\text{R}_{26}$  is a linker.

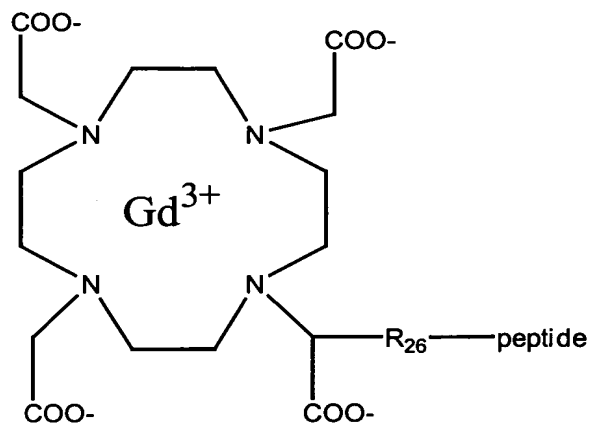
13. An MRI agent according to claim 1 having the formula:



wherein  $\text{R}_{26}$  is a linker.

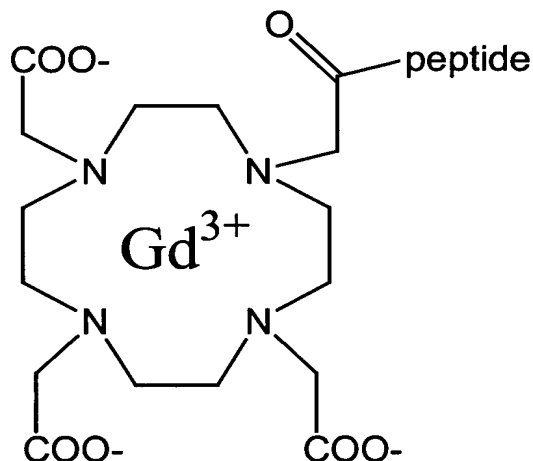
Serial No.: 09/405,046  
Filed: 27 September 1999

14. An MRI agent according to claim 1 having the formula:



wherein  $\text{R}_{26}$  is a linker.

15. An MRI agent according to claim 12, 13 or 14 wherein  $\text{R}_{26}$  comprises  $-(\text{CO}(\text{CH}_2)_n)-$ .
16. An MRI agent according to claim 12, 13 or 14 wherein  $\text{R}_{26}$  comprises  $-(\text{CH}_2)\text{CO}-$ .
17. An MRI agent according to claim 16 having the formula:



18. An MRI agent according to claim 12, 13, or 14 wherein said peptide inhibits a protease.
19. An MRI agent according to claim 18 wherein said protease is selected from the group consisting of caspase, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase.